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Chapter 8

Is there an indication for digital subtraction angiography in the assessment of irradiation-induced vascular damage prior to free flap surgery by the means of the internal mammary vessels?

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Summary

Introduction: Secondary breast reconstruction is increasingly performed after postmastectomy radiotherapy. Damage to blood vessel walls is one of the adverse effects of irradiation therapy, which may jeopardize reconstructive free flap surgery. It would be of great value to be informed about the quality of the recipient vessel prior to reconstructive surgery. The aim of this study was to prospectively assess the value of pre-operative angiography in the assessment of radiation-induced arterial damage and to relate the findings to the degree of vascular damage found during the operation and with histology.

Material & Methods: Women, who had been treated with thoracic radiotherapy and required free flap breast reconstruction, were included. Pre-operative angiographic, intraoperative vessel quality and histological findings of vessels were scored and compared, together with the occurrence of postoperative complications.

Results: In 34 patients a total of 40 free flaps breast reconstruction were performed. Twenty-one internal mammary arteries had been within the field of irradiation. In only two out of six patients with aberrant angiographies the internal mammary artery has been within the field of irradiation.

Conclusion: The damage to the internal mammary vessels cannot always be detected pre-operatively by angiography, or even by intraoperative examination.

Introduction

Free flap reconstructive surgery is often performed after oncologic resections and adjuvant irradiation therapy.⁽¹⁾ Already in 1899 it was reported that irradiation can lead to arteritis and atherosclerotic disease,⁽²⁻⁶⁾ and the overall incidence of radiation-related vascular damage in general ranges from 30% to 89%.^(7,8)

To date, the accuracy of detection of irradiation damage of arteries with angiography prior to free flap reconstructions has not been assessed. Hence, the aim of this study was to prospectively assess the value of pre-operative angiography in the assessment of radiation-induced arterial damage and to relate the findings to the degree of vascular damage found during the operation and with histology. For this purpose we choose to study the internal mammary artery (IMA) in patients scheduled for free flap mammary reconstruction after radiotherapy to the thoracic region.

Materials and Methods

The Institutional Review Board of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, approved this study. Patients gave their written informed consent for the study.

From October 2003 through March 2007, highly selective digital subtraction angiography of the internal mammary arteries (IMA) was preoperatively performed in 34 female candidates for free deep inferior epigastric perforator (DIEP) flap mammary reconstruction. Clinical and treatment data were extracted from the patients' medical and radiotherapy chart and radiation dose plan was used to determine the actual radiation dose delivered to the internal mammary vessels.

A radiologist blinded for the history of the patients scored the angiographies for the anatomy and course of the IMA and its degree of intra-luminal atherosclerotic changes.

During free flap breast reconstruction the internal mammary arteries and veins (IMV) were dissected by removing the overlying medial part of the rib. Before performing the anastomosis in the subcostal space

the vessels were scored for quality of their wall and lumen diameter. Representative 5 mm specimens of both the IMA and the deep inferior epigastric arteries of 25 patients were obtained. All specimens were fixed in 1% paraformaldehyde for 48 hours after which 4 µm thick paraffin embedded cross sections were made. The sections were stained with hematoxylin and eosin and with Lawson's elastin stain.(9) Because irradiation may cause a thickening of the media or intima with simultaneous decrease of the luminal diameter in medium-sized arteries,(10,11) the wall-to-lumen area ratio and the media-to-lumen area ratio were calculated.(9) In this measurement the vessel wall was defined as intima and media. All measurements and calculations were done by one investigator (S.H.).

Statistical analysis

Combining the radiological, intra-operative, and histological observations, we calculated the correlation between the results of the various observations, using the chi-square test to assess the predictive value of the angiography for radiation-related vascular damage and surgical outcome. Statistical significance was accepted at $p - \text{value} \leq 0.05$. Distinction was made between internal mammary vessels that had received the full therapeutic radiation dose at the position of the internal mammary vessels, and those that had not.

Patient characteristics

The 34 women had a mean age of 45 years (range 32 - 60 yrs) and all had previously undergone mediastinal radiotherapy for Hodgkin lymphoma ($n = 2$) or unilateral thoracic radiotherapy because of breast cancer ($n = 32$), a mean of 3.77 years (range 0.5 - 17 yrs) before angiography. The mean total dose had been 43.69 Gy (range 17.5-50.0 Gy). In 19 of the 32 unilaterally irradiated patients, the internal mammary vessels had been included within the field of radiation. 30 of our 34 patients (36 out of 40 flaps) were treated with chemotherapy prior to breast reconstruction.

A bilateral internal mammary angiography was performed in 31 women. Unilateral angiography of only the irradiated IMA was performed in the remaining three patients. Thus, a total of 65 IMA's were depicted angiographically.

In all 34 women, free flap breast reconstruction was performed unilaterally ($n = 28$) or bilaterally ($n = 6$). An in vivo assessment of the vessels at 21 previously irradiated internal mammary recipient sites and 19 previously non-irradiated recipient sites could be made by the surgeon performing the microsurgery. For the histological assessment technically insufficient slides had to be excluded, leaving a total of 14 irradiated and 11 non-irradiated specimens of the IMA's and 27 non-irradiated specimens of the deep inferior epigastric arteries.

Results

1. Correlation between internal mammary angiography and previous radiotherapy

The anatomy, course and contrast-filling diameter of the IMA was scored as normal on 60 of the 65 angiographies. Twenty-one of these 60 IMA's had previously received the full dose of radiation. Three of the five remaining arteries that were scored as angiographically aberrant had previously not been irradiated (Table 1).

Because just 40% of the angiographically aberrant arteries and 35% of the angiographically normal arteries had been irradiated, we conclude that radiation therapy does not correlate with angiographically obvious damage to the IMA ($p > 0.2$).

Table 1
Correlation between pre-operative angiographic findings (n = 65) and parasternal irradiation therapy
(number of aberrant angiographies per side)

Angiographic findings	Parasternal irradiation	No parasternal irradiation
Narrowing	0	3
Deviation of vessel course	2	0
Normal	21	39

2. Correlation between internal mammary angiography and intra-operative observations

Of the 40 arteries, that could be assessed intra-operatively, 37 did not show macroscopic changes of the vascular wall or diameter. In one of the remaining three cases there was an evident intra-luminal plaque and in the other two there were mild fibrotic changes with increased stiffness of the arterial wall (Table 2). There was no correlation between the preoperative angiographic findings and the intra-operative observations of the arteries ($p > 0.2$).

Tabel 2
Comparison between intra-operative finding of the internal mammary artery (IMA) and preoperative angiographic findings and preoperative parasternal irradiation therapy
(Number of reconstructed sides; n = 40)

Operative findings	Aberrant angiography	Normal angiography	Parasternal irradiation	No parasternal irradiation
Mild fibrosis IMA	1	1	1	1
Extended fibrosis IMA/ intraluminal plaque	0	1	0	1
Normal IMA	4	33	20	17

3. Correlation between radiotherapy and intra-operative observations

We found no significant correlation between the intraoperative findings on the internal mammary vessels and exposure to previous radiation ($p > 0.2$). Arterial wall fibrosis was observed in one of the irradiated internal mammary vessels and two of the non-irradiated receptor arteries (Table 2).

The IMV's showed a macroscopically normal vascular wall in 28 of the 40 recipient sites (Table 3). Because of internal mammary venous insufficiency, the microsurgeons switched to using the jugular vein ($n = 1$) or the cephalic vein ($n = 1$) for the venous anastomosis in two of the twelve cases, which exhibited abnormalities. As for the arteries, there was no significant correlation ($p > 0.2$) between intra-operative venous macroscopical appearance and previous radiation exposure (Table 3).

Table 3
Correlation between intra-operative finding of the internal mammary vein (IMV) and preoperative parasternal irradiation therapy (number of reconstructed sides; $n = 40$)

Operative findings	Parasternal irradiation	No parasternal irradiation
Small diameter IMV	0	3
Brittle wall of IMV	4	2
Mild fibrosis IMV	1	2
Normal IMV	16	12

4. Comparison of histological vessel measurements between irradiated and non-irradiated arteries.

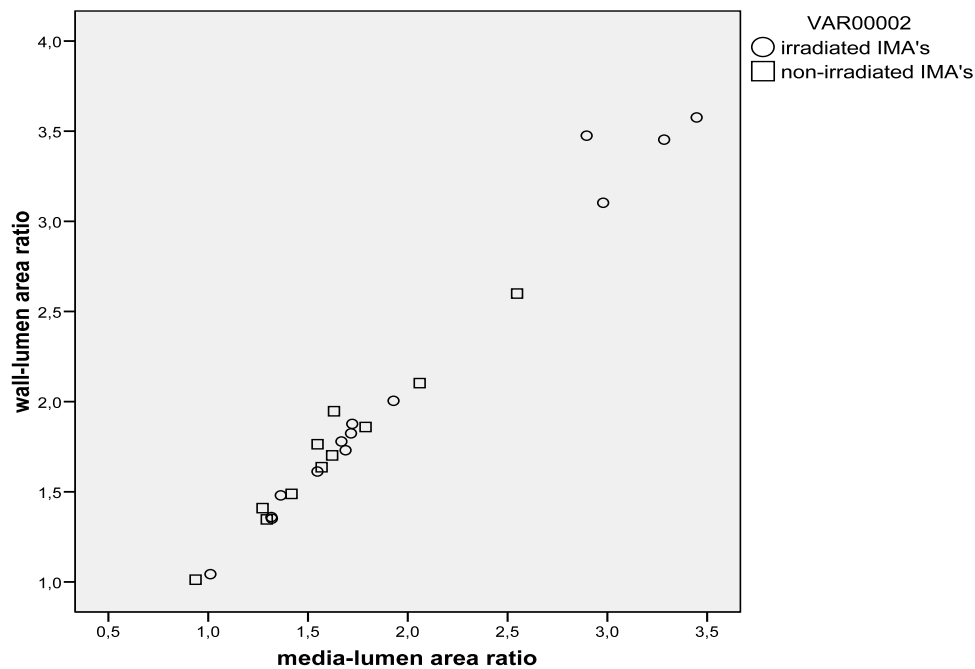
There were no significant differences in mean “wall-to-lumen area ratio” between the irradiated IMA, non-irradiated IMA and the IEA, and neither in their mean “media-to-lumen area ratio” (Table 4). Comparing the media-lumen and the wall-lumen area ratio of irradiated and non-irradiated IMA's graphically (Figure), it was apparent that both ratios were nearly congruent in both groups. Of the three patients, who underwent bilateral breast reconstruction with just one of the IMA's being irradiated, no significant difference in wall-to-lumen area ratio could be found between the irradiated and the non-irradiated IMA.

Table 4
Wall-to-lumen and media-to-lumen area ratios of irradiated ($n = 14$) and non-irradiated ($n = 11$) internal mammary arteries (IMA) and the inferior epigastric arteries (IEA) in the pedicle of the flaps ($n = 27$)

	Wall-to-lumen area ratio		Media-to-lumen area ratio	
	Mean	SD	Mean	SD
Irradiated IMA	2.12	0.88	1.99	0.80
Non-irradiated IMA	1.72	0.42	1.61	0.43
IEA of DIEP-flap	2.31	1.23	2.25	1.16

Figure

Graph comparing media-lumen and wall-lumen area ratios of irradiated and non-irradiated IMA's



5. Correlation between internal mammary angiographic findings and outcome of surgery

A total of 40 free flaps were transplanted in 34 patients. Thirty-three breast reconstructions were free of complications (Table 5). There were seven postoperative flap complications, leading to complete flap loss in four of them (10%). Five of the seven complicated breast reconstructions were associated with a normal angiography. Hence, the preoperative angiographic findings did not correlate with the surgical outcome ($0.1 > p > 0.05$).

Of those two patients with an aberrant angiography and a postoperative complication, one patient had a combined arterial and venous thrombosis resulted in total flap loss after revision. This patient had shown a medial deviation of the IMA on the preoperative angiography but intraoperative, macroscopic inspection of the internal mammary vessels had not revealed any vascular disorder. The other patient had a partial fat necrosis, while the pre-operative angiography had shown a small lumen of the IMA but this could not be confirmed during surgery.

Table 5

Correlation between postoperative complications and preoperative angiographic findings and pre-operative parasternal irradiation therapy (number of reconstructed sides, n = 40)

Postoperative complications	Aberrant angiography	Normal angiography	Parasternal irradiation	No parasternal irradiation
Venous thrombosis with successful re-anastomosis	0	2	1	1
Venous thrombosis with unsuccessful reanastomosis and flap loss	0	2	1	1
Arterial and venous thrombosis with unsuccessful reanastomosis and flap loss	1	0	1	0
Too fragile vessels for anastomosis with flap loss	0	1	1	0
Partial fat necrosis	1	0	0	1
None	3	30	17	16

6. Correlation between previous radiotherapy and outcome of surgery

Seventeen of the 33 uneventful breast reconstructions and four of the seven complicated breast reconstructions were in the group of previous radiotherapy to the internal mammary vessels (Table 5). Hence, there was no statistical significant correlation between the two ($p > 0.2$).

Discussion

Even though irradiation may induce atherosclerotic narrowing in areas unusual for the natural occurrence of arterial disease,(12) only few authors studied the possible irradiation-related damage of the IMA as a source of free flap failure.(13) Likewise, reports on the outcome of IMA-grafts in cardiac revascularisation surgery in patients with a history of thoracic radiation therapy are sparse. Some of these reports suggest that the irradiated IMA is unsuitable for cardiac grafting,(14,15) whereas other studies found no adverse effects on revascularization outcome.(16-18)

We found that internal mammary chain radiotherapy does not always cause angiographic or macroscopically obvious damage to the IMA. Furthermore, it was not possible to preoperatively predict postoperative complications on the basis of internal mammary angiography. Still, we found some correlation between previous radiotherapy and postoperative complications, but no significant or specific correlation between such irradiation and total flap loss.

Potential shortcomings of our study

Because we only performed arterial angiographies, it was not possible to assess the IMV's preoperatively. To image the IMV an extra venography via the sternum or a CT-scan would have been necessary. To depict the veins the patients would have had to be exposed to extra radiation and the risk

of complications.(19-20) Therefore in our study a normal angiography does not rule out possible surgical insufficiency of the IMV, which might be better depicted by duplex sonography.

Second, our series are too small to distinguish between short-term and long-term prevalence of radiation effects.

Last, we did not reckon with possible vascular damage induced by chemotherapy. Still, because 30 of our 34 patients (36 out of 40 flaps) were treated with chemotherapy prior to breast reconstruction no statistically significant observations could have been made from such data.

Quality of internal mammary vessels

In unirradiated IMA's atherosclerotic changes are rare. The incidence of atherosclerotic changes detected by angiography in literature ranges from 0% to 11.1%.(21-25) and the incidence of histologically proven arterial stenosis has been found to vary from 4.2% to 12.4%.(26,27) Still, none of the 215 specimen of the study by Kay et al.(26) and only one specimen in a series of 160 patients studied by Sisto and Isola(27) showed more than a 50% reduction in lumen diameter of the internal mammary artery.

Hardly any data are available on the incidence of atherosclerosis in series of irradiated IMA's. As such van Son et al. reported on four patients with radiation-induced coronary artery disease in whom internal mammary angiography was performed.(16) The IMA was judged not patent in two patients and, in both, histological examination confirmed dense fibrosis of the IMA-wall with complete obliteration of the lumen. The arteries of the other two patients showed a slightly thickened adventitia with minimal signs of fibrosis.

In our study, angiographic changes of the IMA-wall have been found in five out of 65 angiographies (7.7%). Macroscopic changes of the IMA-wall were intraoperatively observed in three out of 40 patients (7.5%). Compared to the literature both prevalences are well within the normal range.(21-27)

Histology of irradiation damage

Grassman was the first to describe vascular lesions of radiodermatitis and noted the swelling and proliferation of the endothelium to the point of projection into the lumen of small arteries.² Irradiation may produce arterial damage varying from intimal thickening, fragmentation of the elastic lamina, overproduction of elastic tissue, chronic inflammation and necrosis of the adventitia, hyaline thickening, to thrombosis and the production of collagen in the larger arteries.(3-5)

Medium-sized arteries such as the IMA are less sensitive to irradiation than blood capillaries,(10-11) but these arteries may still show prominent adventitial fibrosis, subendothelial and intimal accumulation of foam cells, and hyaline deposition in the media as a result of irradiation.(10) Russell et al. described an increase in proteoglycan content of the intima of irradiated IMA vessels compared with unirradiated IMA, from 65% to 73%. However the collagen content between irradiated and unirradiated IMA's was not found to differ significantly.(9)

We were unable to find differences in wall-to-lumen area ratio, or media-to-lumen area ratio in the irradiated arteries and the non-irradiated arteries. Probably, the dose of radiation in our series was relatively low compared to the radiation sensitivity of the IMA; or the follow-up interval was too short. Still, linking the intraoperative observations on the IMV's with prior irradiation therapy, it was our impression that irradiated veins were a bit more brittle than non-irradiated veins.

Discussion of our observations

We observed a low, statistically insignificant correlation between prior irradiation and surgical outcome. But there was no correlation between angiographic aberrances and surgical outcome. This may be explained, as flap survival is not only related to the quality of the IMA and IMV, but is influenced by many more factors, like skills, technique, ischemia, perforator quality and smoking habits of the patient. We found a slight predominance of macroscopically brittle walls among the previously irradiated IMV's. Other intra-operatively observed venous aberrances such as a smaller diameter or mild fibrosis did not correlate with previous radiotherapy.

Our series may be too small to allow a statistically warranted conclusion regarding the correlation between previous radiotherapy exposure of vessels and surgical outcome. Still, it offers a good impression of the lack of correlation between pre-operative angiography, possible irradiation damage to the IMA, and the intraoperative finding.

Conclusion and alternative techniques of vascular evaluation

We conclude that there is no value of pre-operative highly selective digital subtraction angiography in the assessment of the degree of radiation-induced arterial damage and that there is no correlation to the vascular damage found during the operation and with histology. Thus digital subtraction angiography is not helpful as a preoperative assessment tool for the selection of potential candidates for free flap mammary reconstruction. Furthermore, such angiography is expensive and invasive. Although its risk of complications is small, these risks are not negligible as they include, arterial aneurysm at the puncture side (0.4-2.0%), anaphylactic shock resulting from allergy to the contrast medium (0.2-0.4%), superficial phlebitis and edema (17.9%), renal impairment (<2%), and hemorrhagic (11.4%) and thrombotic events (0-4.0%).(28-33) Because of these risks and because we found the subtraction angiography unhelpful, color flow doppler sonography, computer tomography angiography, or magnetic resonance angiography might be better screening methods.(18,22,34,35)

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